REMARKS

I. INTRODUCTION

This communication is submitted in response to the Office Action dated March 10, 2005. Claims 31, 36, 37, 39 and 43-48 are pending in the application. Reconsideration of the application is requested.

II. RESTRICTION REQUIREMENT

At page 2 of the Office Action, the Examiner acknowledged that claims 36-37, 39, 43-45 and 47-48 have been amended to read upon the elected invention. Accordingly, these claims, which were previously withdrawn, have been included in the examination on the merits.

III. PRIOR ART REJECTIONS

In paragraphs 5, 7, and 12 of the Office Action, claims 31, 36, 37, 39 and 43-48 were rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Flynn et al., Biochemistry (1986), Vol. 35, pp. 7308-7315 (Flynn) and Billing-Medal et al., U.S. Patent No. 6,183,952 (Billing). Applicants respectfully traverse these rejections.

Applicants incorporate the arguments raised in previous Amendments, but reiterate here only those points that appear to have been overlooked.

The key point that has not been addressed by the Patent Office is that the prior art did not teach or suggest that the synthetic oligonucleotide having the features recited in Applicants' claims is an inhibitor of DCMTase or otherwise is useful as an anti-cancer agent. It appears the Examiner may be assuming that, because the substrates listed in Table 1 of Flynn "were designed to mimic DNA transcriptional cis elements previously reported to have cytosine C-5 methylated regulation," this suffices to teach that each of these substrates can be used not only as a substrate for DCMTase, but also as an inhibitor of DCMTase activity. Yet, as evidenced by Applicants' data (see Fig. 1B), not all substrates listed in Table 1 of Flynn have this inhibitory activity on DCMTase (see CRE a^{mct}).

The Examiner appears to be confusing "substrate" of DCMTase with "inhibitor" of DCMTase. Those skilled in the art, however, would not consider any substrate of DCMTase to be useful as an anti-cancer or other therapeutic agent. Accordingly, those skilled in the art would not

be motivated to modify the synthetic oligonucleotide of GC-box b^{met} in Table 1 of Flynn to introduce phosphorothioate linkages or to add a pharmaceutically acceptable carrier.

At page 11 of the Office Action, the Examiner argues that "Flynn's explanation on pages 7309-7310 that a precise functional description of the enzyme is essential for understanding how DCMTase [catalyzes the developmentally regulated patterns of DNA] methylation and for the design of novel anticancer strategies based on regulation of the enzyme is seen to be sufficient motivation to modify the internucleotide linkages and provide a pharmaceutical composition as instantly claimed."

At page 6 of the Office Action, the Examiner argues that "obviousness does not require absolute predictability" and implies that Flynn's teaching at pages 7309-7310 is sufficient to provide a reasonable expectation of success. "In the absence of evidence of some unexpected result or limitation that would tip the scales of patentability in applicant's favor, the claimed invention is prima facie obvious." The implication of the Examiner's argument is that every substrate designed to mimic DNA transcriptional cis elements previously reported to have cytosine C-5-methylated regulation is prima facie obvious as an anti-cancer agent. As discussed at page 58, lines 29-31, of Applicant's specification, "GC-box b^{MET} is distinct in form and function from previously described DCMTase inhibitors. There is a need for DCMTase inhibitors that are not incorporated into DNA and that are mechanistically unlike 5-azadeoxycytidine".

There appears to be an inference made by the Examiner at page 10 of the Office Action that the combined teachings of Flynn and Billing may have rendered the claimed GC-box b^{MET} obvious for use as an antisense molecule for inhibiting methylation thereby allegedly motivating modification of GC-box b^{MET} into GC-box p^{MET} or a pharmaceutical salt or composition. Such an inference erroneously presumes that, because Billing teaches preventing the transcription of BU101 polypeptide with a DNA oligonucleotide that is complementary to a ***unique*** region of the gene involved in transcription of that gene, one skilled in the art would have a reasonable expectation that the GC-box b^{MET} oligonucleotide could be used to somehow disrupt DCMTase methylation. Because the Examiner does not set forth an explicit technical basis for how such a disruption would occur, Applicants can only speculate as to the proposed antisense strategy.

Because one skilled in the art would not consider a GC-box a suitable antisense target for disrupting transcription in a specific manner, it is difficult to address the Examiner's inference.

Assuming, however, that the Examiner is basing the rejection on an allegedly obvious use of the claimed GC-box b^{MET} oligonucleotide as an antisense molecule that would bind the GC-box involved in transcription, this allegedly obvious anti-cancer strategy is untenable. Billing suggests use of an oligonucleotide "designed to be complementary to a region of the gene involved in transcription." (See col. 26, lines 31-32.) Billing makes no suggestion or teaching to use an oligonucleotide that is complementary to transcriptional control elements common to numerous genes.

Most genes have GC-box elements in their transcriptional control regions, but their RNA transcripts generally lack such elements. Antisense technologies aim to specifically target and interfere with the translation of proteins by hybridizing to target mRNA, or in the highly unusual case of targeting transcription, by hybridizing to the DNA of chromosomes. Even if targeting nuclear DNA were feasible, the ubiquity of GC-box elements would result in an antisense strategy that disrupts transcription of a massive number of genes. Any inference that the claimed synthetic oligonucleotides provide an obvious antisense strategy for inhibiting DCMTase activity naively relies on an erroneous assumption that a technically reasonable level of specificity (not to mention access and efficacy) could be attained.

Applicants' claimed invention is based on a previously unknown and unexpected mechanism of inhibiting DCMTase via an allosteric site (on the enzyme, not on the DNA). The Flynn 1996 paper only describes GC-box a/b^{MET} as a substrate for the enzyme, and makes no suggestion that these substrates could serve to inhibit the enzyme. The wishful speculation in Billing (at column 26) that the diagnostic probes for breast cancer described therein could somehow be used to inhibit transcription of this breast cancer marker, and the further wish that such inhibition would actually serve as an anti-cancer treatment, cannot possibly suffice to motivate one skilled in the art to try, let alone expect success, in an anti-cancer strategy that relies upon use of Applicants' claimed synthetic oligonucleotides as antisense molecules disrupting transcription at GC-box elements.

Applicants urge the Examiner to consider that, to the extent the claimed oligonucleotide may appear an obvious choice as a pharmaceutical composition, this could only be through the benefit of hindsight, and without taking into account how little was known about the mechanisms of DCMTase inhibition at the time the present application was filed.

IV. CONCLUSION

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

GATES & COOPER LLP
Attorneys for Applicant(s)

Howard Hughes Center
6701 Center Drive West, Suite 1050
Los Angeles, California 90045
(310) 641-8797

Date: May 9, 2005

By: _____
Name: Karen S. Canady
Reg. No.: 39,927

KSC/bjs/amb